Bloody Pericardial Effusion in Patients With Cardiac Tamponade
Is the Cause Cancerous, Tuberculous, or Iatrogenic in the 1990s?

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Study objectives: The decrease in incidence of tuberculosis, along with the increase in invasive cardiovascular procedures, may have changed the frequency of causes of bloody pericardial effusion associated with cardiac tamponade, although this is not yet recognized by medical textbooks. We analyzed the causes of bloody pericardial effusion in the clinical setting of cardiac tamponade in the 1990s; patients' survival; the effect of laboratory results on discharge diagnosis; and how often bloody pericardial effusion is a presenting manifestation of a new malignancy or tuberculosis.

Design: Retrospective, observational, single-center study.

Setting: A community hospital.

Patients: The charts of all patients who underwent pericardiocentesis for cardiac tamponade and had bloody pericardial effusion were retrospectively reviewed.

Results: Of 150 patients who had pericardiocentesis for relieving cardiac tamponade, 96 patients (64%) had a bloody pericardial effusion. The most common cause of bloody pericardial effusion was iatrogenic disease (31%), namely, secondary to invasive cardiac procedures. The other common causes were malignancy (26%), complications of atherosclerotic heart disease (11%), and idiopathic disease (10%). Tuberculosis was detected as a cause of bloody pericardial effusion in one patient and presumed to be the cause in another patient. Bloody pericardial effusion was found to be a presenting manifestation of a newly diagnosed malignancy in two patients. The patients in the idiopathic and iatrogenic groups were all alive and had no recurrence of pericardial effusion at 24 ± 27 and 33 ± 21 months after hospital discharge, respectively, whereas 80% of patients with malignancy-related bloody effusions died within 8 ± 6 months.

Conclusions: In a patient population that is reasonably representative of that in most community hospitals in the United States, the most common cause of bloody pericardial effusion in patients with signs or symptoms of cardiac tamponade is now iatrogenic disease. Of the noniatrogenic causes, malignancy, complications of acute myocardial infarction, and idiopathic disease predominated. Hemorrhagic tuberculous pericardial effusions are uncommon and may likely reflect a low incidence of cardiac tuberculosis in community hospitals in the United States.

Key words: iatrogenic disease; pericardial effusion; pericardium; tuberculosis

Abbreviations: LDH = lactate dehydrogenase; TB = tuberculosis

The principal causes of bloody pericardial effusion have evolved substantially in the past 3 decades. In the 1960s, hemopericardium associated with cardiac tamponade was most commonly related to rupture of a syphilitic or dissecting aneurysm of the aorta, whereas 20 years later it was most commonly associated with myocardial infarction, malignancy, and tuberculosis (TB).1–11 The cause and prognostic significance of cardiac tamponade associated with bloody pericardial effusion has not been reviewed in the 1990s. We therefore reviewed the records of patients who have undergone therapeutic pericardiocentesis because of cardiac tamponade in a single
medical center since the beginning of 1991, with the goal of establishing the current cause, clinical characteristics, and survival pattern of patients with bloody pericardial effusion.

**Materials and Methods**

The Institutional Review Board approved the study. The charts of patients who were admitted to Cedars-Sinai Medical Center between May 1, 1991, and August 31, 1997, were identified by a computer search for pericardiocentesis and cardiac tamponade. One hundred fifty cases with sufficient data to determine the gross appearance and the cause of the pericardial effusion were identified. Pericardial fluid had been routinely analyzed for gross appearance, cell count, glucose, total protein, lactate dehydrogenase (LDH), and cytology as well as cultures for bacteria and mycobacterium. The total volume of the evacuated fluid was also recorded. Pericardial biopsy was performed at the discretion of the attending physician.

Only the patients with bloody or serosanguineous effusions were included in this analysis. The criteria used for classification of the pericardial fluid as well as the definition of transudative and exudative pericardial fluids are presented in Table 1. Demographic data, medical history, hospital course, and laboratory results were obtained from the hospital chart. A follow-up on patients’ survival, current medical status, and recurrence of pericardial effusion was performed by a review of the medical center computer database and by a telephone follow-up with the patient’s attending physician.

### Results

Of the 150 patients with pericardiocentesis and cardiac tamponade, 54 (36%) had nonhemorrhagic pericardial effusions, and 96 (64%) had hemorrhagic effusions. In each case, pericardiocentesis was performed because of signs or symptoms of pericardial tamponade. In this report, we analyzed in detail the 96 patients with bloody pericardial effusions. The group included 47 women, aged 59 ± 20.5 years (range, 24 to 90 years), and 49 men, aged 61 ± 21.5 years (range, 24 to 87 years).

**Clinical and Imaging Studies Findings**

Average symptom duration was 6 ± 10 days (range, 1 to 42 days). Clinical presentation of the patients was not different from that of prior studies. The most common presenting symptoms were dyspnea (69%) and chest pain (39%). Other common presenting symptoms were palpitations (16%), fatigue (13%), and fever (11%). The most common physical findings were tachycardia (63%), low pulse pressure (39%), and jugular venous distention (33%). Pulsus paradoxus was noted in only 22% of cases in which it was specifically recorded. The most common ECG findings were low QRS voltage (51%), PR-segment depression (27%), and atrial fibrillation (25%). The chest radiograph showed cardiomegaly in 70% of the patients, pleural effusions in 56%, and atelectasis in 29%. In addition to presence of a moderate to large pericardial effusion, echocardiography most commonly revealed right atrial collapse in 55% of patients, left atrial collapse in 15%, and right ventricular collapse in 34%.

### Cause of Pericardial Effusion

The cause of bloody pericardial effusion is summarized in Table 2. An iatrogenic cause was the most common cause of bloody pericardial effusion (31%). Pericardial effusions associated with the postpericardiotomy syndrome were found in 12 patients (13%) at an average of 45 days after surgery. Among the remaining 56 patients, malignancy (26%), complications of acute myocardial infarction (11%), and idiopathic disease (10%) accounted for 70% of the cases. Three patients had HIV infection—one patient had chronic renal failure and was on hemodi-

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### Table 1—Definitions and Classification of Etiologies of Bloody Pericardial Effusion*

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Bloody effusion</td>
<td>Nonclotting red fluid that did not become clear after the withdrawal of the first 20 mL of the effusion, with a RBC count ≥ 100,000/μL³</td>
</tr>
<tr>
<td>Malignant</td>
<td>A histologically confirmed cancer, or finding of malignant cells in cytological examination of the effusion</td>
</tr>
<tr>
<td>Complication of MI</td>
<td>LV free wall rupture, thrombolytic therapy or due to insertion of transvenous pacemaker within 3 days of MI</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Positive culture of the fluid</td>
</tr>
<tr>
<td>Uremic</td>
<td>A patient on hemodialysis or serum creatinine &gt; 3.0 mg/dL</td>
</tr>
<tr>
<td>Traumatic</td>
<td>Chest trauma within the preceding 24 h</td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td>INR &gt; 3.5 on day of admission with no other attributable etiology of bloody pericardial effusion</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>The etiology of the effusion could not be determined from the chart or by the attending physician; or a viral etiology was suspected but could not be confirmed by laboratory tests</td>
</tr>
<tr>
<td>Postpericardiotomy</td>
<td>&gt; 1 week and &lt; 3 months after cardiac surgery</td>
</tr>
<tr>
<td>Exudative effusion</td>
<td>Fluid total protein &gt; 3.0 gr/dL or fluid to serum total protein ratio &gt; 0.5; or fluid LDH &gt; 300 u/dL; or fluid to serum LDH ratio &gt; 0.6</td>
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</tbody>
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*MI = myocardial infarction; LV = left ventricle; INR = international normalized ratio.
alyses, one patient with lymphoma had a positive culture for *Staphylococcus aureus* from the effusion, and one patient had tuberculous pericarditis diagnosed on autopsy. One patient with a medical history of tuberculous pericarditis had a recurrence of pericardial effusion and was treated with antituberculosis therapy despite negative pericardial cultures. Three patients with systemic lupus erythematosus had chronic renal failure. Two patients taking warfarin had international normalized ratio levels that were above the therapeutic range (2 to 3.5) on the day of hospital admission with cardiac tamponade, and subsequently had no other attributable cause of cardiac tamponade at discharge.

**Survival**

Data on survival were available for 91 of the 96 patients. None of the patients with an iatrogenic cause died within an average of 33 ± 21 months from pericardiocentesis (excluding patients with postpericardiotomy syndrome). Nineteen of 25 patients (76%) with malignancy-related effusions died within an average time of 8 ± 6 months of pericardiocentesis, whereas 4 patients (2 of whom had lymphoma, with a follow-up of up to 64 months) were alive 35 ± 25 months after hospital discharge (range, 9 to 64 months). In 2 patients, follow-up data were not available. One patient with a primary diagnosis of heart failure, included in the idiopathic group, died during the initial hospital stay. The other nine patients with an idiopathic cause were all alive at 24 ± 27 months after hospital discharge (longest follow-up, 78 months), and none had recurrence of pericardial effusion on follow-up.

**Laboratory Evaluation**

The criteria for exudative and transudative pericardial effusions used in our study were previously defined by Meyers et al and are presented in Table 1. Of 55 patients who had bloody effusion with symptoms > 24 h duration, 41 patients (75%) had an exudative effusion and 10 patients (18%) had transudates by both fluid protein and LDH concentrations. Four cases (7%) in which fluid protein level was > 3.0 g/dL and LDH was < 300 U/L, were classified as exudates. There was no difference in survival between the exudate and transudate groups: 14 patients (35%) in the exudate group and 3 patients (30%) in the transudate group died within 8 ± 6 months of pericardiocentesis.

The average volume of the fluid evacuated during pericardiocentesis was 796 ± 482 mL in patients who had symptoms for > 24 h. The largest effusions had a malignant cause, with breast cancer patients having an average effusion volume of 1,120 ± 385 mL.

The cytology of the effusion was positive for malignant cells in six patients with a previous diagnosis of malignancy. In two patients, the cytology of the pericardial fluid was positive for adenocarcinoma of the lung, and cardiac tamponade was the initial manifestation of their malignancy. Two patients with systemic lupus erythematosus had lupus erythematosus cells in their effusions. Two patients had *Staphylococcus aureus* cultured from the pericardial effusion: one patient had pneumonia and the other was a patient infected with HIV who had non-Hodgkin’s lymphoma. The results of the laboratory tests changed the diagnosis made before pericardiocentesis in three patients: two patients who had a newly diagnosed lung cancer and one patient who had a diagnosis before pericardiocentesis of tuberculous pericarditis that was not confirmed by acid-fast staining or culture of the effusion fluid. Nevertheless, this patient was treated for a presumptive diagnosis of tuberculous pericarditis.

**Discussion**

The principal finding of our study is that the cause of bloody pericardial effusion associated with cardiac tamponade has changed substantially in the past decade. The most common cause is now iatrogenic disease. In the noniatrogenic group, malignancy, complications of atherosclerotic heart disease and idiopathic causes account for three fourths of the cases. Nonetheless, as presented in Table 3, the most widely referenced textbooks still regard malignancy

### Table 2—Etiology of Bloody Pericardial Effusion Associated With Cardiac Tamponade*

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. (%)</th>
</tr>
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<tbody>
<tr>
<td>Iatrogenic</td>
<td>30 (31)</td>
</tr>
<tr>
<td>Transcatheter interventions, pacemaker insertion</td>
<td>18 (18)</td>
</tr>
<tr>
<td>Postpericardiotomy syndrome</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>25 (26)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Complications of acute myocardial infarction</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Iatrophic</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Uremic</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Trauma</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Bacterial or parainfectious</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Anticoagulant therapy</td>
<td>2 (2)</td>
</tr>
<tr>
<td>TB</td>
<td>2 (2)</td>
</tr>
<tr>
<td>SLE</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Rejection post heart transplantation</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>96 (100)</td>
</tr>
</tbody>
</table>

*SLE = systemic lupus erythematosus.*
Robbins Pathologic Basis of Disease (1994) “An exudate composed of blood mixed with a fibrinous or suppurative effusion is most commonly caused by tuberculosis or by direct malignant neoplastic involvement of the pericardial space.”

The Principles and Practice of Medicine (1996) “The most common cause of hemorrhagic pericardial effusion in Western countries is disease caused by TB.”

The Principles and Practice of Medicine (1996) “TB-associated hemorrhagic pericardial tamponade among the 96 cases analyzed. One case was diagnosed by the finding of granulomas in the pericardium on autopsy. Another patient had a presumptive diagnosis of TB based on a medical history of tuberculous pericarditis.”

Harrison’s Principles of Internal Medicine (1998) “Bloody fluid is commonly due to tuberculosis or tumor.”

Meyers et al (1998) “The fluid may be a transudate or an exudate and is often serosanguineous in neoplastic, tuberculosis...”

Emergency Medicine Concepts and Clinical Practice (1996) “Serosanguineous effusions are most commonly associated with neoplasms, tuberculosis...”

and TB as the primary causes of hemorrhagic pericardial effusion. In fact, 70% of our cases with bloody pericardial effusion are not associated with either cancer or TB. The change to iatrogenic disease as a major cause of cardiac tamponade was previously described by Hayes and Danielson and probably parallels the increase in catheter-based diagnostic and therapeutic cardiovascular procedures in the last decade. A review of studies published since 1981 reveals that cardiac surgery and catheter-based cardiac procedures have increasingly become a major cause of cardiac tamponade. In the series of patients described by Hayes and Danielson, cardiac surgery and catheter-related complications accounted for 28% of cases of cardiac tamponade. Moreover, in a recently published article from the same institution, 9.6% of echocardiographically guided pericardiocenteses were performed in the catheterization laboratory because of cardiac perforation. It is yet to be clarified whether this change in causes has also resulted in an increase in the total number of cases of cardiac tamponade.

Referral bias may be a potential limitation of our analysis. Although this limitation cannot be eliminated, it can be analyzed, based on the sample area of our hospital. Our hospital is a community hospital in an urban area and serves a heterogeneous population of patients. It has active infectious diseases, oncology, rheumatology, and nephrology services. It also serves as a referral center for invasive percutaneous cardiac procedures and cardiac surgery. Moreover, during the last 5 years, we had 3,500 admissions because of AIDS, and each year culture-positive TB is diagnosed in 15 to 20 patients. We also treat a large population of patients who are at risk for TB, namely, immunocompromised, chronically ill, and elderly patients. Thus, we believe that our patient population is representative of that of an urban community in the western world.

Although one patient with constrictive pericardial disease caused by TB was identified at our hospital, the past year we have found only two cases of TB-associated hemorrhagic pericardial tamponade among the 96 cases analyzed. One case was diagnosed by the finding of granulomas in the pericardium on autopsy. Another patient had a presumptive diagnosis of TB based on a medical history of tuberculous pericarditis. In the recent series published by Meyers et al on the usefulness of diagnostic tests on pericardial effusion, all 110 effusion cultures were negative for mycobacterium. The low incidence of TB as a cause for bloody pericardial effusion is consistent with other studies over the last 2 decades from Europe and the United States showing a decrease in the prevalence of tuberculous pericardial disease.

The pericardium is known to be the major site of cardiac involvement in AIDS patients. However, as was previously described by Reilly et al in a series of autopsies of patients with AIDS, 7 of 58 autopsies showed pericardial effusion, but only two patients had clinical pericarditis before death. A review of 643 AIDS patients found only 16 patients (2%) to have pericardial infection, and only 9 patients (1%) had mycobacterial infection. Moreover, signs and symptoms of cardiac tamponade develop in only one third of AIDS patients with clinical pericarditis. AIDS may in fact blunt the inflammatory response to infection, and thus it is possible that there will be a low incidence of cardiac tamponade in patients with concomitant AIDS and TB. The patients in our series all had signs and symptoms of cardiac tamponade, which may explain the absence or paucity of TB and AIDS cases.

Sixty-four percent of all patients who presented at our hospital in cardiac tamponade had bloody pericardial effusions. In a recent study, hemorrhagic or serosanguineous pericardial effusions were found in 72% of patients, and all postpericardiotomy, rheumatologic, and traumatic effusions were bloody. Yet it has been reported that pericardial effusions caused by rheumatologic or postpericardiotomy syndrome may be either clear, serosanguineous, or bloody.
Bloody pericardial effusion was the presenting manifestation of a malignancy in two patients (2%) in our study. This has been described in prior case reports.\textsuperscript{20,26,27} This low frequency presumably reflects the improvement of imaging and diagnostic methods in the last 2 decades that leads to detection of malignancy before development of cardiac tamponade in most patients.

There are only two previously published studies on the long-term follow-up of patients with pericardial effusion.\textsuperscript{20,28} and there are no data on the survival of patients with hemorrhagic pericardial effusion. Our results show that the survival of patients with bloody pericardial effusions is determined by the diagnosis made before pericardiocentesis. Among patients in the iatrogenic group, none died acutely and all were alive on a long-term follow-up (33 ± 21 months). Approximately 80% of patients with a previously known malignancy died within 8 months of the pericardiocentesis. In contrast, all the patients with an idiopathic bloody pericardial effusion except one with congestive heart failure were alive on an average follow-up of 24 months.

Whereas “therapeutic” pericardiocentesis had a higher yield than “diagnostic” pericardiocentesis (29% vs 6%) in a study performed by Permanyer-Miralda et al\textsuperscript{29} nearly 2 decades ago, our study, along with other recently published studies,\textsuperscript{12,16,25} casts some doubt on the value of routine diagnostic tests on the effusion fluid. In the series published by Meyers et al,\textsuperscript{12} among 110 mycobacterial, 62 viral, and 120 fungal cultures of pericardial effusion, there was no positive result. In our study, the diagnosis before pericardiocentesis was changed by the analysis of pericardial fluid in only 3 of 96 patients, and only 12 patients (12%) had any positive findings in their pericardial fluid. Of these 12 patients, the analysis of the pericardial fluid significantly affected management in only 3 patients. From these data, it is evident that an extensive diagnostic evaluation of pericardial fluid has a low yield of positive results. Nevertheless, laboratory analysis of a bloody pericardial effusion seems warranted, especially in patients at risk of intrapericardial infection such as immunocompromised patients, and in patients who present with fever of unknown origin. Thus, a simplified approach such as spinning-down a sample of pericardial fluid for cytology and performing acid-fast and Gram’s staining and routine culture may be more cost-effective.

In summary, in a patient population that is reasonably representative of that in most community hospitals in the United States, the most common cause of bloody pericardial effusion in patients with signs or symptoms of cardiac tamponade is now iatrogenic disease. The most frequent noniatrogenic causes of bloody pericardial effusion are malignancy, atherosclerotic heart disease, and idiopathic disease. TB appears to be uncommon as a cause of bloody pericardial effusions associated with tamponade in the community setting. Nonetheless, TB should not be excluded as a treatable form of bloody pericardial effusion, particularly in those at high risk for infection. Analysis of pericardial fluid adds little if anything to the diagnosis, and patients with an idiopathic bloody pericardial effusion have a good long-term prognosis.

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